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14. ABSTRACT The major hypothesis is that prior occupational exposure to polychlorinated biphenyls (PCBs) results in decrements in neuropsychological and neurological performance and the number of dopamine (DA) terminals in the basal ganglia determined by ß-CIT SPECT imaging. Data collection is complete (a comprehensive questionnaire, examinations and SPECT imaging). PCBs and thyroid hormones have been measured in serum and bone lead has been determined. Results, obtained using ß-CIT SPECT imaging demonstrate a significant negative relationship between current serum PCB concentrations and decreases in the density of ß-CIT binding only in women. Serum PCB concentrations have decreased 10-fold from peak values during occupational PCB use, but remain elevated (two-fold) compared to a similar-aged non-occupationally exposed population. Estimating PCB half lives using analysis of both current and archived serum samples revealed significantly longer half lives for PCB congeners of occupational origin in women compared to men. Data analysis and manuscript preparation continues for neurological and neuropsychological endpoints.

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INTRODUCTION

The major hypotheses to be tested in this project are that high-level occupational exposure of former capacitor workers to polychlorinated biphenyls (PCBs) will result in reductions in: (i) performance on neuropsychological and neurological tests that reflect the historic PCB body burden of the individual and (ii) the number of dopamine (DA) terminals in the basal ganglia.

Aging former capacitor workers, previously employed at capacitor manufacturing facilities located approximately fifty miles north of Albany, NY; underwent neuropsychological and neurological exams; completed a comprehensive occupational, residential and dietary questionnaire; had blood drawn to measure serum thyroid hormone and PCB concentrations, and underwent a non-invasive test to determine bone lead concentrations in Albany, NY. This latter measure will reduce the likelihood of confounding the neurological effects of prior PCB exposure with the neurological effects of prior lead exposure. Finally, approximately 40% of the subjects participated in a second portion of the study that used brain β-CIT SPECT imaging to determine whether prior occupational exposure to PCBs reduces the number of basal ganglia DA terminals. Imaging took place at the Institute for Neurodegenerative Disorders in New Haven, CT under the supervision of Dr. Kenneth Marek.

Results, obtained using β-CIT SPECT imaging, demonstrate a significant negative relationship between current serum PCB concentrations and decreases in the density of β-CIT binding only in women. These findings are supported by epidemiological data demonstrating increased Parkinson's disease mortality, again only in women (Steenland *et al*., *Epidemiology* **17**(1), 8-13, 2006).

Analysis of serum PCB concentrations in samples obtained from all participants in this study revealed a level of 6.6 ppb (geometric mean, wet weight basis), which represents a 10-fold decrease from historic levels reported in the same population in the late 1970s, but still a level nearly double that reported in a similar-aged non-occupationally exposed population (Fitzgerald *et al*., Environmental Health Perspectives 116(2), 209-215, 2008). In addition, archived serum PCB concentrations were determined in a subset (N=45) of the study population for whom archived samples from the 1970s were available. The PCB data from the current and archived serum samples allows us a unique opportunity to model PCB half-lives using a time interval of nearly 30 years.

STUDY INVESTIGATORS

Albany, NY Based Testing

Richard F. Seegal - Wadsworth Center, New York Sate Dept. of Health (NYSDOH): Principal Investigator

Edward F. Fitzgerald - University at Albany, School of Public Health: Epidemiologist

Lenore J. Gensburg - University at Albany, School of Public Health: Tracing, Screening, Residential, Occupational, Dietary and Medical Histories

Eric S. Molho, Donald S. Higgins - Albany Medical Center: Neurological Assessment

Stewart A. Factor - Emory University: Neurology Consultant

Robert J. McCaffrey - University at Albany: Neuropsychological Assessment

Richard F. Haase - University at Albany: Biostatistician

Mary S. Wolff - Mount Sinai School of Medicine: Serum PCB Analyses

Andrew C. Todd - Mount Sinai School of Medicine: Bone Lead Determination

Patrick Parsons - Wadsworth Center, NYSDOH: Bone Lead Determination

New Haven, CT Based Testing

Kenneth Marek, John P. Seibyl, Danna Jennings - Institute for Neurodegenerative Disorders: ß-CIT SPECT Brain Imaging

PROGRESS IN FISCAL YEAR 2008

The following narrative details the progress we have made in the ongoing data analysis during the seventh year of the project. Data collection ended in April 2006; we provide below a table of final tracing, screening and participation rates (see Table I). At the conclusion of data collection, we had tested 241 subjects in Albany which represents 97% of our projected goal of testing 248 subjects. In addition, 89 of those subjects traveled to New Haven, CT to undergo β-CIT imaging to estimate the density of basal ganglia dopamine transporters. This number represents 93% of our stated goal of testing 96 subjects.

Significant effort has been made, and continues to be made, to analyze the vast amounts of data that were generated during active data collection. In addition to collecting the major dependent variables (neurological, neuropsychological, β-CIT, bone lead, thyroid hormone and serum PCB concentrations) we also collected extensive information from a 2-2.5 hour interview on potential confounders that may influence the dependent variable outcomes listed above. Interview data pertaining to demographic characteristics, medical history, medication use, smoking and alcohol consumption and diet (including consumption of sport-caught fish) and other relevant variables have been double data entered and subdivided into subject-specific SAS datasets. Edit programs have been developed to detect out-of-range and logical inconsistencies and any errors have been corrected. The occupational histories have been reviewed by two certified industrial hygienists who evaluated each job for the likelihood of exposure to PCBs, lead, mercury, and pesticides, using a four point scale. Each job has also been classified using Standard Industrial and Occupation codes and medications have been coded according to the American Hospital Formulary Service.

Table I. Tracing, screening and participation outcomes among former capacitor factory workers from Fort Edward and Hudson Falls, New York (N=2,844)

Tracing Outcome	**N**	**%**
Eligible for screening	1124	39.52
Not eligible for screening		
Living	256	9.00
Dead	844	28.68
Unlocatable	577	20.29
End of Study	43	1.51
Screening Outcome	**N**	**%**
Eligible for participation	484	43.06
Not eligible for screening		
Medically ineligible	348	30.96
Other ineligible	50	4.45
Refused		
After screening interview	110	9.79
Refused screening interview	42	3.74
Passively	80	7.12
End of Study	10	0.89
Participation Outcomes	**N**	**%**
Participation in Albany, NY Portion of Study	241	49.79
Participation in New Haven, CT Portion of Study	89	36.93

Table II compares the demographic and background characteristics of all study participants with the cohort for whom archived serum samples were available. Significant differences between males and females within each cohort, as well as significant differences between the cohorts, are noted in the below table. Out of a total of 241 participants, 129 (53.5%) were men and 112 (46.5%) were women. The mean age of the participants was 64.4 years, with a range from 50 to 87. There were no significant differences in mean age between the men (64.1 years) and the women (64.7 years).

Table II. Demographic and background characteristics of all study participants (N=241) and the cohort of subjects with archived sera (N=45)

Characteristic	All Study participants N [a]	% or Mean (SD)	Archived Sera Cohort N [a]	% or Mean (SD)
Gender				
Male	129	53.6	33	73.3
Female	112	46.5	12	26.7
Income				
<15,000	20	9.0	1	2.2
15,000-30,000	50	22.4	17	37.8
30,000-45,000	59	26.5	7	13.3
45,000-60,000	42	18.8	7	15.6
60,000-75,000	29	13.0	7	15.6
>75,000)	23	10.3	0	0
Marital status				
Married or live with partner	165	70.5	30	73.2
Divorced, never married, separated, or widowed	69	29.5	11	26.8
Lost weight in past year				
No	189	80.8	33	80.5
Yes	45	19.2	8	19.5
Had hepatitis or cirrhosis of the liver				
No	225	97.0	39	97.5
Yes	7	3.0	1	2.5
Age (years)				
Male	129	64.1 (8.1)	33	64.0 (7.8)
Female	112	64.7 (9.3)	12	70.5 (8.6)*
Education (school years completed)				
Male	122	13.1 (2.2)++	29	12.7 (1.2)+
Female	112	12.4 (1.7)	12	12.2 (0.9)
BMI (kg/m^2)				
Male	122	29.1 (4.5)	29	28.6 (3.9)+
Female	112	29.9 (6.1)	12	25.9 (3.5)**
Number of cigarette packs in the previous year				
Male	122	38.4 (111.4)	29	44.1 (116.1)
Female	112	46.6 (122.8)	12	121.8 (179.9)
Number of cigarette packs in the last 10 years				
Male	122	630 (1404)	29	557 (1191)+
Female	112	867 (1946)	12	2100 (3169)
Total number of drinks/week in the last year				
Male	122	6.84 (9.16)+++	29	8.24 (9.9)+
Female	112	1.47 (3.46)	12	1.86 (4.0)
Total number of drinks/week in the last 10 years				
Male	122	7.01 (9.38)+++	29	8.50 (9.35)++
Female	112	1.14 (2.62)	12	1.05 (1.37)
Number of births (females only)	112	2.71 (1.63)	12	3.75 (2.14)*
Total weeks lifetime breastfeeding (females only)	112	7.18 (22.73)	12	6.92 (20.59)

[a] Number of observations varies across characteristics due to missing values;
* The T-test or ChiSq is significant at p <0.05 for all study participants vs. archived sera cohort;
** The T-test or ChiSq is significant at p <0.01 for all study participants vs. archived sera cohort;
+ The T-test or ChiSq is significant at p <0.05 for male vs. female;
++ The T-test or ChiSq is significant at p <0.01 for male vs. female;
+++ The T-test or ChiSq test is significant at p <0.001 for male vs. female.

Table III lists current serum PCB concentration for all study participants expressed on a wet weight basis and lipid adjusted basis for individual PCB congeners as well as totals for light and heavy PCB congeners (defined as eluting before or after DDE (dichlorodiphenyldichloro-ethylene)) respectively. The geometric mean total serum PCB concentration for all subjects was 6.65 ppb on wet weight basis and 1.02 ppm on a lipid-adjusted basis. For males the corresponding values were 7.47 ppb and 1.19 ppm, and 5.81 ppb and 0.86 ppm for females. Congeners that are markers for occupational exposure include PCB-28, PCB-74, PCB-118, PCB-105 and PCB-156 and are identified below. After more than 30 years, mean PCB levels are approximately two fold higher in these former capacitor workers than in individuals of similar age who resided in the same towns, but did not work at the capacitor plants or any job that entailed PCB exposure.

Table III. Current serum PCB concentrations of all study participants (N=241)

IUPAC number	IUPAC structure	Wet Weight (ppb) Geometric Mean	SD	Lipid-Basis (ppm) Geometric Mean	SD
Light PCBs [b]					
PCB-28 [a]	2,4,4'	0.09	1.11	0.01	0.19
PCB-74 [a]	2,4,4',5	0.76	5.70	0.12	1.03
PCB-66	2,3',4,4'	0.17	0.34	0.03	0.06
PCB-56	2,3,3',4'	0.10	0.23	0.02	0.04
PCB-101	2,2',4,5,5'	0.27	0.42	0.04	0.07
PCB-99	2,2',4,4',5	0.15	0.43	0.02	0.08
Total Light PCBs		**2.57**	**6.91**	**0.40**	**1.26**
Heavy PCBs [c]					
PCB-118 [a]	2,3',4,4',5	0.19	0.91	0.03	0.18
PCB-146	2,2',3,4',5,5'	0.07	0.28	0.01	0.05
PCB-153	2,2',4,4',5,5'	0.81	1.82	0.12	0.34
PCB-105 [a]	2,3,3',4,4'	0.04	0.19	0.01	0.04
PCB-138	2,2',3,4,4',5'	0.63	1.92	0.10	0.37
PCB-178	2,2',3,3',5,5',6	0.03	0.09	0.005	0.02
PCB-187	2,2',3,4',5,5',6	0.13	0.21	0.02	0.04
PCB-183	2,2',3,4,4',5',6	0.06	0.06	0.01	0.01
PCB-167	2,3',4,4',5,5'	0.03	0.11	0.004	0.02
PCB-174	2,2',3,3',4,5,6'	0.05	0.05	0.01	0.01
PCB-177	2,2',3,3',4,5',6'	0.04	0.07	0.01	0.01
PCB-156 [a]	2,3,3',4,4',5	0.15	0.74	0.02	0.14
PCB-172	2,2',3,3',4,5,5'	0.06	0.09	0.01	0.02
PCB-180	2,2',3,4,4',5,5'	0.44	0.96	0.07	0.17
PCB-170	2,2',3,3',4,4',5	0.19	0.50	0.03	0.09
PCB-199	2,2',3,3',4,5,5',6'	0.10	0.14	0.01	0.02
PCB-203	2,2',3,4,4',5,5',6	0.09	0.10	0.01	0.02
Total Heavy PCBs		**3.66**	**7.53**	**0.56**	**1.43**
Total PCBs		**6.65**	**13.22**	**1.02**	**2.48**

[a] Markers for occupational exposure;
[b] Elute before DDE;
[c] Elute after DDE.

Table IV presents the relationship of current serum PCB concentrations (log adjusted, lipid basis) with key characteristics of study participants. Age was the demographic variable most strongly associated with log serum total PCB concentrations (β=0.015, $p \leq 0.001$). Total PCB concentrations were higher among men than women (β=0.176, $p \leq 0.001$) and among persons with less education (β=-0.022, p=0.041). BMI was positively related to log serum PCB concentrations, but this association was statistically significant only for the light congeners (β=0.012, p=0.032).

Table IV. Multivariate regression analysis of current serum PCB concentration (log adjusted, lipid basis) on demographic and background characteristics (N=233)

	Light PCBs[a]			Heavy PCBs[b]			Total PCBs		
	β	p-value	R^2	β	p-value	R^2	β	p-value	R^2
Age (years)	0.009	0.009	0.03	0.019	0.0001	0.25	0.015	0.0001	0.15
Gender (female)	-0.156	0.009	0.03	-0.168	0.0001	0.08	-0.176	0.0001	0.07
Education (school years complete)	-0.031	0.032	0.02	-0.017	0.060	0.02	-0.022	0.041	0.02
BMI (kg/m^2)	0.012	0.032	0.02	0.002	0.577	0.00	0.007	0.090	0.01

[a] Elute before DDE: PCB-28, PCB-74, PCB-66, PCB-56, PCB-101, PCB-99;
[b] Elute after DDE: PCB-118, PCB-146, PCB-153, PCB-105, PCB-138, PCB-178, PCB-187, PCB-183, PCB-167, PCB-174, PCB-177, PCB-156, PCB-172, PCB-180, PCB-170, PCB-201, PCB-203.

Table V presents the geometric means of the 1976 and 2004 PCB values, expressed on a wet weight basis, for the five occupational congeners, their light, heavy, and total sums, and the light, heavy, and total PCB values (the sum of all 23 congeners) shown separately for men and women and combined by gender for the 45 study participants in the archived sera cohort for whom we had serum PCB concentrations available at both time points**.** Serum total PCB concentrations for men and women combined, decreased significantly from a geometric mean of 37.8 ppb in 1976 to 9.8 ppb currently ($p \leq 0.001$; F=95.16; df=1,44). The relative decline was greater for the occupational light congeners (geometric mean of 21.3 ppb to 2.8 ppb) than for the occupational heavy congeners (geometric mean of 2.7 ppb to 0.9 ppb). Serum PCB concentrations measured in 2004 (current) were significantly higher in women than men for congeners of occupational origin, light and heavy summed PCBs—an effect most likely due to the lower 1976 serum levels seen in women compared to men and the inverse relationship between initial serum levels and half-lives.

Table V. Geometric mean of current and archived PCB concentrations (wet weight, ppb) in sera from study participants in the archived cohort (N=45) [a]

PCB Congener or Summed Score	1976 Male and Female Combined	2004 Male and Female Combined	1976 Male	2004 Male	1976 Female	2004 Female
Occupational PCBs[b]						
PCB28	11.27	0.17	12.13	0.11	9.23	0.49
PCB74	7.75	2.29	8.67	1.74	5.71	4.89
PCB105	0.58	0.14	0.68	0.12	0.36	0.24
PCB118	1.71	0.42	1.69	0.32	1.77	0.91
PCB156	0.21	0.23	0.24	0.21	0.15	0.30
Occupational Summed PCBs						
Occupational Light	21.27	2.80	23.20	2.15	16.77	5.79
Occupational Heavy	2.74	0.92	2.78	0.76	2.62	1.55
Occupational Total	24.56	3.86	26.56	3.05	19.80	7.44
Summed PCBs[c]						
Light PCBs	26.41	4.28	28.82	3.58	20.76	6.98
Heavy PCBs	9.08	5.05	9.01	4.42	9.27	7.29
Total PCBs	37.82	9.80	40.37	8.38	31.62	15.05

[a] Total N=45 (33 males and 12 females) in 1976 and in 2004.
[b] Occupational Light = PCB28 + PCB74. Occupational Heavy = PCB105 + PCB118 +PCB156. Occupational Total = Occupational Light + Occupational Heavy.
[c] Summed PCBs are the sum of all occupational (PCB congener numbers 28, 74, 105, 118, and 156) and non-occupational (PCB congener numbers 66, 56, 101, 99, 146, 138, 178, 187, 183, 167, 174, 177, 153, 172, 180, 170, 201, and 203) PCB congeners.

Table VI presents the half-lives of the occupational congeners, the sums of the light, heavy, and total occupational congeners along with the light, heavy, and total PCBs based on the full set of 23 congeners. The half-lives of the heavily chlorinated PCBs for men and women combined (33.1 years) are more than 3-times longer than for the lightly chlorinated congeners (10.7 years). A similar pattern is observed when only the occupational congeners are considered with half-lives of the heavy congeners (17.8 years) approximately twice the average for the light PCBs (9.6 years). There are also gender differences with women exhibiting half-lives ranging from 1.5- to 3-times longer than that of men. The longer half-lives for all categories of PCB congeners in women, compared to men, most likely reflects the higher initial concentrations of PCBs in the men and the fact that congener half-lives are inversely related to initial serum concentrations.

This finding, that the half-life of a congener is indirectly related to its initial concentration is further supported by data presented in Table VII which shows the half-lives according to whether the 1976 concentrations were above or below ("high" or "low", respectively) the median serum PCB values for each group. These data indicate that PCB half-lives are longer among the low exposure group than in the high exposure group, with half-lives varying by a factor of 1:2 to 1:10. Most importantly, this relationship (*i.e.*, an inverse relationship between initial exposure levels and half-life estimates) was seen for congeners of occupational origin.

Table VI. Geometric means of half-lives of PCBs in years (calculated using wet weight data) for study participants in the archived cohort (N=45)[a]

PCB Congener or Summed Score	Half-life Males and Females Combined	Half-Life Males	Half-Life Females
Occupational PCBs[b]			
PCB28	4.6	4.2	6.6
PCB74	15.9	12.1	124.9
PCB105	13.7	10.9	46.5
PCB118	13.8	11.6	29.2
Occupational Summed PCBs			
Occupational Light	9.6	8.2	18.2
Occupational Heavy	17.8	14.9	37.2
Occupational Total	10.5	9.0	19.8
Summed PCBs[c]			
Light PCBs	10.7	9.3	17.8
Heavy PCBs	33.1	27.2	81.1
Total PCBs	14.4	12.4	26.2

a Total N=45 (33 males and 12 females) in 1976 and in 2004.
b Occupational Light = PCB28 + PCB74. Occupational Heavy = PCB105 + PCB118 +PCB156. Occupational Total = Occupational Light + Occupational Heavy.
c Summed PCBs are the sum of all occupational (PCB congener numbers 28, 74, 105, 118, and 156) and non-occupational (PCB congener numbers 66, 56, 101, 99, 146, 138, 178, 187, 183, 167, 174, 177, 153, 172, 180, 170, 201, and 203) PCB congeners.

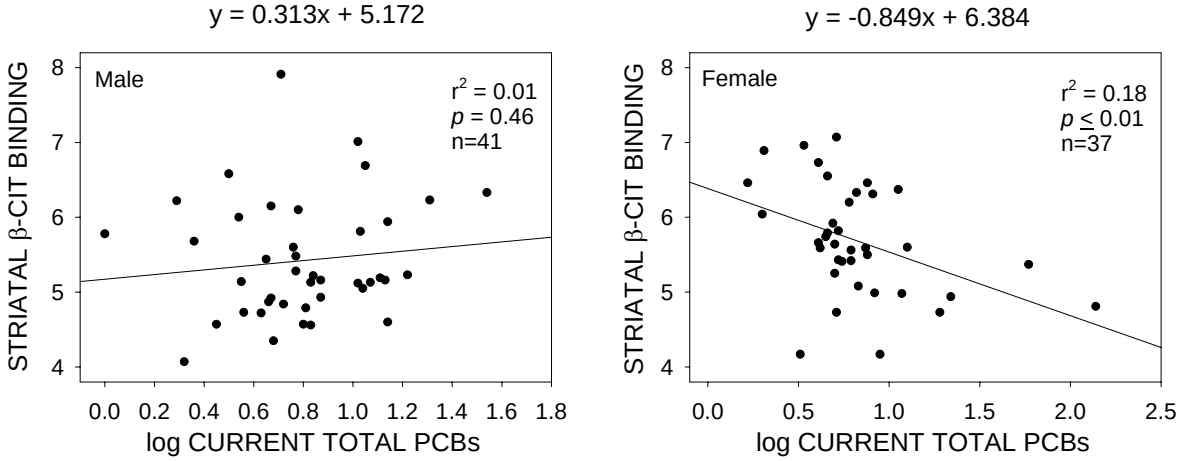
T**able VII**. Geometric mean of 1976 and 2004 concentrations and half-lives for high and low 1976 total PCB exposure groups from archived cohort (N=45)[a]

PCB Congener or	1976 Low	2004 Low	Half-Life Low	1976 High	2004 High	Half-Life High
Occupational PCBs[b]						
PCB28	4.62	0.20	6.13	28.65	0.14	3.67
PCB74	2.94	1.47	28.10	21.36	3.63	10.95
PCB105	0.23	0.09	19.92	1.49	0.23	10.35
PCB118	0.76	0.30	21.28	4.00	0.59	10.10
PCB156	0.11	0.18	-35.59	0.45	0.30	50.94
Occupational Summed PCBs						
Occupational Light	8.13	1.94	13.56	58.16	4.11	7.32
Occupational Heavy	1.26	0.70	32.65	6.14	1.22	12.01
Occupational Total	9.47	2.71	15.52	66.49	5.59	7.84
Summed PCBs[c]						
Light PCBs	10.32	3.19	16.51	70.52	5.84	7.79
Heavy PCBs	5.22	4.32	102.95	16.18	5.94	19.36
Total PCBs	16.12	7.72	26.35	92.28	12.58	9.74

a Total N=45 (33 males and 12 females) in 1976 and in 2004; N = 23, low exposure (1976 TPCBs ≤ 36.534 (median)) and N = 22 and high exposure (1976 TPCBs > 36.534 (median)).
b Occupational Light = PCB28 + PCB74. Occupational Heavy = PCB105 + PCB118 +PCB156. Occupational Total = Occupational Light + Occupational Heavy.
c Summed PCBs are the sum of all occupational (PCB congener numbers 28, 74, 105, 118, and 156) and non-occupational (PCB congener numbers 66, 56, 101, 99, 146, 138, 178, 187, 183, 167, 174, 177, 153, 172, 180, 170, 201, and 203) PCB congeners.

We report that the significant statistical relationship between dopamine transporter density, measured by β-CIT SPECT imaging, and current serum total PCB concentrations, observed only in female former capacitor workers is not altered after controlling for potential confounders (age, body mass index, smoking, alcohol consumption, caffeine consumption, bone lead density and the use of cardiovascular medicines). PCB levels were measured in serum from the subjects at the time of imaging. This data, presented in Figure 1, represents the average uptake of the radio-labeled ligand [^{123}I]β-CIT in the putamen and caudate of male and female former exposed workers measured by SPECT imaging, providing an *in*-vivo measure of dopamine transporter density. These data, suggesting a greater susceptibility of women to neurological changes associated with PCB exposure, are supported by the finding of Steenland *et al.* (*Epidemiology* **17**(1), 8-13, 2006) who reported greater Parkinson's disease mortality in women from the same cohort. Most interestingly, recent findings by Lin *et al.* (*Environmental Health Perspectives* **116**(2), 184-189, 2008) also support a gender difference in susceptibility to halogenated hydrocarbons. These authors reported cognitive deficits only in women, but not in men who had been exposed to contaminated rice oil that contained PCBs and dibenzofurans.

Figure 1. Dopamine Transporter Density Measured by β-CIT SPECT Imaging as a function of Current Serum PCB Concentrations



We have started analysis of the relationship between neurological and neuropsychological outcomes and the exposure variables serum PCB and bone lead concentrations. A surprising preliminary finding is the relationship between bone lead and a number of the neuropsychological outcomes after controlling for potential covariates. In total, 23 variables were evaluated as potential covariates with four key covariates (age depression level, gender and education) remaining in the final model. Multiple linear regression analysis found an effect from bone lead in 9 out of 20 neuropsychological tests with 5 out of 9 memory and learning tests and 3 out of 9 motor function tests affected. In addition, multiple linear regression analysis found more neurological tests that were significant in females than in males. This finding is consistent with the significant statistical relationship reported above between dopamine transporter density, measured by β-CIT SPECT imaging, and current serum total PCB concentrations, observed only in female former capacitor workers. Again, the findings of Lin *et al.*, who reported cognitive deficits only in women, but not in men, who had been exposed to rice oil contaminated with halogenated hydrocarbons, supports a gender difference in the susceptibility to toxicants.

KEY RESEARCH ACCOMPLISHMENTS

As in all epidemiological studies, presentation of results prior to controlling for potential confounders (*e.g.*, age, gender, life style [smoking, alcohol and drug use], and medications) that may affect the dependent variables of interest is premature.

We present in Tables II-VII, a significant portion of the data and results from a manuscript entitled "Estimating Half-Lives of PCB Congeners in Former Capacitor Workers Measured Over a Twenty-Eight Year Interval" which is almost ready for submission for publication in *Journal of Exposure Science and Environmental Epidemiology*. These data show that serum PCBs levels in a population of former capacitor worker have, on average, declined nearly 10-fold, but remain elevated with average levels double that of an age-matched non-occupationally exposed cohort. Current serum PCB concentrations were significantly and positively associated with the age of the subject(s), their body mass index and inversely associated with the number of years of education. Finally, women had significantly longer half-lives for PCB congeners of occupational origin, as well as total PCBs, than did men.

We also report in Figure 1 that the significant statistical relationship between dopamine transporter density, measured by β-CIT SPECT imaging, and current serum total PCB concentrations which is observed only in female former capacitor workers is not altered after controlling for potential confounders (age, body mass index, smoking, alcohol consumption, caffeine consumption, bone lead density and the use of cardiovascular medicines). These findings are currently being prepared for submission for publication in *Experimental Neurology*. Similar statistical analyses are currently being conducted to analyze the relationships between exposure to PCBs and other major neurological and neuropsychological dependent variables.

REPORTABLE OUTCOMES

During the past year I have presented and discussed findings from this study at two scientific meetings: the first as an invited discussion leader for the scientific session: 'Gene-Environment Interaction in Neurodegenerative Disease' at the Gordon Research Conference: Mechanisms of Toxicity in Lewiston, ME in July 2008; and the second presenting a talk entitled "Does Reproductive Senescence Alter Gender Differences in PCB-Induced Changes in Central Dopaminergic Function" as an invited participant at the 25th International Neurotoxicology Conference: Environmental Etiologies of Environmental Disorders in Rochester, NY in October 2008.

We anticipate a series of publications summarizing the major findings of the project. At this time two manuscripts are almost ready for submission for publication. The first manuscript entitled "Estimating Half-Lives of PCB Congeners in Former Capacitor Workers Measured Over a Twenty-Eight Year Interval" will be submitted to *Journal of Exposure Science and Environmental Epidemiology*. This manuscript reports current serum PCB concentrations in a population of former capacitor workers and compares the levels to the levels measured in archived serum samples from a subset of the workers when PCBs were still in occupational use. This data is then used to estimate half-lives for selected PCB congeners of occupational origin over a twenty-eight-year interval.

The second manuscript entitled "Occupational Exposure to PCBs Differentially Affects Basal Ganglia Dopamine Terminal Densities in Men and Women: A β-CIT Imaging Study" reports on the unexpected statistically significant finding of gender differences in the relationship between dopamine transporter density, measured by β-CIT SPECT imaging, and current serum total PCB concentrations which is observed only in female former capacitor workers will be published in *Experimental Neurology*.

Additional publications will address the association between both current and estimated historical serum PCB levels and the major health endpoints of the study neurological and neuropsychological measures. We anticipate that the appropriate co-investigators will serve as senior authors for these manuscripts.

CONCLUSIONS

We have come very close to our originally stated goals for recruiting and testing subjects, both in Albany, NY and in New Haven, CT and are proud of this progress since many of our subjects were elderly and had to travel considerable distances to undergo testing at these two sites.

The significant negative relationship seen only in female workers—all of whom were postmenopausal—has allowed us to formulate a hypothesis that estrogen withdrawal increases risk of basal ganglia dopamine dysfunction only in women. This unexpected finding is supported by a recent publication by Steenland *et al.* (*Epidemiology* **17**(1), 8-13, 2006) that demonstrated increased Parkinson's disease mortality only in female former capacitor workers and supports our original hypothesis that, in a manner similar to that seen in PCB-exposed adult non-human primates, PCBs reduce dopamine function in the basal ganglia. Indeed, these findings led to the successful awarding of an NIH grant to Seegal to study the role of gender and ovarian hormones in influencing PCB-induced changes in brain dopamine function.

We continue to show that current serum PCB levels are significantly elevated in former capacitor workers compared to literature values for non-occupationally exposed individuals. There are several major findings evident from the analyses of current serum PCB concentrations in this cohort of former capacitor workers.

First, as we previously reported, current serum PCB concentrations were significantly associated with cumulative years of occupational exposure with the associations stronger for the occupational congeners than the non-occupational congeners, confirming that congeners such as PCB-28, 74, 105 118 and 156 are indeed unique markers of exposure in this cohort. In addition, the associations with the occupational light congeners were strongest for exposure during the years that Aroclor 1016 were used, whereas the associations with exposure to Aroclor 1242 were similar for both light and heavy occupational congeners. These findings probably reflect that the fact that Aroclor 1016 is comprised mostly of light congeners while 1242 is mixture of both light and heavy congeners. In contrast to the results for occupational exposure, serum PCB concentrations were not associated with the reported consumption of fish from bodies of fresh water in New York State. The lack of an effect for fish consumption may reflect the fact that relatively few persons in this cohort ate fish from the Hudson River and Lakes Ontario and Champlain, the most heavily contaminated bodies of water in New York State. The results nevertheless confirm that the major source of PCB exposure in this cohort is occupational.

The second major finding regarding current PCB concentrations is that the mean levels were two-fold higher in these former capacitor workers than in individuals of similar age who resided in the same towns but did not work at the capacitor plants. This latter finding—that PCB levels remain elevated more than thirty years after the last direct occupational exposure to PCBs occurred—testifies to the high level of exposure that had occurred in those plants and the long half-life of many PCB congeners. In addition, current serum PCB concentrations were significantly and positively associated with the age of the subject(s), their body mass index and inversely associated with the number of years of education.

Finally, the half-lives of the heavily chlorinated PCBs for men and women combined are more than 3-times longer than for the lightly chlorinated congeners. A similar pattern is observed when only the occupational congeners are considered with half-lives of the heavy congeners approximately twice the average for the light PCBs. There are also gender differences with women exhibiting half-lives ranging from 1.5- to 3-times longer than that of men. The

longer half-lives for all categories of PCB congeners in women, compared to men, most likely reflects the higher initial concentrations of PCBs in the men and the fact that congener half-lives are inversely related to initial serum concentrations.

This finding, that the half-life of a congener is indirectly related to its initial concentration is further supported by data which shows the half-lives according to whether the 1976 concentrations were above or below ("high" or "low", respectively) the median serum PCB values for each group. These data indicate that PCB half-lives are longer among the low exposure group than in the high exposure group, with half-lives varying by a factor of 1:2 to 1:10. Most importantly, this relationship (*i.e.*, an inverse relationship between initial exposure levels and half-life estimates) was seen for congeners of occupational origin.

APPENDIX

Invited Meetings and Presentations

Invited discussion leader for the scientific session: 'Gene-Environment Interaction in Neurodegenerative Disease' at the Gordon Research Conference: Mechanisms of Toxicity; Lewiston, ME, July 2008

Presented 'Does Reproductive Senescence Alter Gender Differences in PCB-Induced Changes in Central Dopaminergic Function' as an invited participant serving on the Conference Program Committee at the 25th International Neurotoxicology Conference: Environmental Etiologies of Environmental Disorders, Rochester, NY, October 2008.